Prediction of Regression and Relapse of Endometrial Hyperplasia With Conservative Therapy

Ioannis D. Gallos, Raji Ganesan, and Janesh K. Gupta

OBJECTIVE: To identify predictors and to estimate their prognostic accuracy for regression and relapse of endometrial hyperplasia treated with levonorgestrel-releasing intrauterine system or oral progestogens.

METHODS: This was a cohort study of women treated with levonorgestrel-releasing intrauterine system or oral progestogens for complex hyperplasia or atypical complex hyperplasia for women wishing to preserve their fertility or those who were unfit for surgery. Hazard ratios (HRs) with the Cox proportional hazards model and Kaplan-Meier survival estimates for independent predictors were calculated.

RESULTS: Regression was evaluated in 344 women over a 12-year period, with a median follow-up of 58.8 months (interquartile range 38.4–96.4, range 12–148.2) for levonorgestrel-releasing intrauterine system compared with 95.1 months (interquartile range 41.6–124.6, range 13.2–162) for oral progestogens. In women treated with levonorgestrel-releasing intrauterine system for complex hyperplasia, we found that 221 women regressed (96.5%, 221/229) and body mass index (BMI) 35 or higher was associated with failure to regress (HR 5.51, 95% confidence interval [CI] 1.05–28.87; P=.043). Relapse was evaluated in 219 women over a 9-year period, with median follow-up of 67 months (interquartile range 50.4–103.5, range 14.5–146.4) for levonorgestrel-releasing intrauterine system and 96.8 months (interquartile range 62.3–122, range 6–151.5) for oral progestogens. In women treated with levonorgestrel-releasing intrauterine system for complex hyperplasia, we found that 18 women experienced relapse (12.7%, 18/142) and BMI 35 or higher was found to be a strong independent predictor of relapsed endometrial hyperplasia (HR 18.93, 95% CI 3.93–91.15; P<.001). Only 3.3% of women with complex hyperplasia treated with levonorgestrel-releasing intrauterine system and with BMI less than 35 experienced relapse during long-term follow-up compared with 32.6% of women with BMI 35 or higher.

CONCLUSION: Body mass index 35 or higher is strongly associated with failure to regress and relapse of complex hyperplasia treated with levonorgestrel-releasing intrauterine system.

(Obstet Gynecol 2013;121:1165–71)
DOI: 10.1097/AOG.0b013e31828cb563

LEVEL OF EVIDENCE: II

Endometrial hyperplasia is diagnosed three times more commonly than endometrial cancer, and it can progress to cancer if left untreated.[1] Without intervention, the risk of progression to carcinoma is less than 1% for women with simple hyperplasia, 3% for complex nonatypical hyperplasia, and up to 29% for women with atypical complex hyperplasia.[2] A survey found that more than 85% of clinicians treat complex nonatypical hyperplasia with levonorgestrel-releasing intrauterine system or oral progestogens.[3] For women with atypical complex hyperplasia, hysterectomy is the indicated treatment because up to 43% of women have concomitant carcinoma.[4] However, it may not be possible for all women given its potential risks, especially for older or obese patients and those with significant comorbidities. Medical management therefore is advocated in such cases. In observational studies, it has been found that endometrial hyperplasia regression occurs often with oral progestogens and even more often with levonorgestrel-releasing

See related editorial on page 1155.

From the School of Clinical and Experimental Medicine, University of Birmingham, Birmingham Women's Hospital, and the Department of Histopathology, Birmingham Women's Hospital, Birmingham, United Kingdom.

The authors thank Wilma Arnold for administrative support.

Corresponding author: Ioannis D. Gallos, MD, Nuffield Department of Obstetrics and Gynaecology, Oxford Radcliffe Hospitals NHS Trust, The Women's Centre, Oxford OX3 9DU, United Kingdom; e-mail: ioannis.gallos@nhs.net.

Financial Disclosure
Funded by a grant from Wellbeing of Women (ELS022). Dr. Gallos is supported by a grant from Wellbeing of Women (ELS022). The other authors did not report any potential conflicts of interest.

ISSN: 0029-7844/13

intrauterine system (Mirena).[5,6] In a recent study, we also found that women with endometrial hyperplasia treated with levonorgestrel-releasing intrauterine system or oral progestogens often experience relapse after their initial regression, and this occurs more often with oral progestogens than with levonorgestrel-releasing intrauterine system.[7]

In 1989, Ferenczy et al[8] described 85 women with complex nonatypical hyperplasia treated with oral progestogens. It was found that women with cytologic atypia were less likely to achieve endometrial regression and also were more likely to experience relapse during follow-up. Our current knowledge is that body mass index (BMI, calculated as weight (kg)/[height (m)]^2), age, menopause, and diabetes are associated with endometrial hyperplasia.[9] These also could represent prognostic markers for the outcomes of endometrial regression or relapse of endometrial hyperplasia treated conservatively, but these have not yet been investigated. In this study, our objective was to identify predictors and to estimate their prognostic accuracy for regression and relapse of endometrial hyperplasia treated with levonorgestrel-releasing intrauterine system or oral progestogens.

MATERIALS AND METHODS

This was a comparative cohort study. We recruited all women with complex nonatypical hyperplasia or atypical complex hyperplasia diagnosed and who underwent treatment with levonorgestrel-releasing intrauterine system or oral progestogens in a tertiary referral hospital in Birmingham, United Kingdom. Recruitment for women treated with levonorgestrel-releasing intrauterine system started in August 1998. For women treated with oral progestogens, prospective recruitment started in August 2008. Women with complex nonatypical hyperplasia and atypical complex hyperplasia treated with oral progestogens from August 1998 to August 2008 were invited for long-term follow-up in our clinic and have been followed-up ever since. These women were identified through a central electronic histopathology database, which includes all patients with endometrial hyperplasia diagnosed in our hospital for the study with no missing patients. The histopathologic diagnoses were undertaken by two experienced gynecologic pathologists working independently; referral to the other pathologist for a second opinion was made in cases in which there was diagnostic doubt, and a mutual consensus was then achieved. Women were reviewed in our gynecology outpatient clinic after diagnosis and were offered levonorgestrel-releasing intrauterine system, oral progestogens, or hysterectomy as part of our routine clinical practice. Since August 2008, women opting for oral progestogen treatment were prescribed either norethisterone 5 mg three times per day continuous or medroxyprogesterone 10 mg twice per day continuously for 6 months. Women with atypical complex hyperplasia diagnosed were counseled and offered a hysterectomy. Women who declined surgery or who were medically unfit to undergo surgery were offered levonorgestrel-releasing intrauterine system or oral progestogens. Study participants underwent regular outpatient clinic review and endometrial histologic surveillance by outpatient endometrial sampling. Histologic surveillance was performed on a 6-month basis for the first 2 years and yearly thereafter for 5 years, and then the patients were given a choice to have continued yearly surveillance. Women who did not adhere to this strategy were invited for clinic review to obtain long-term follow-up outcome. Ethical approval from the Coventry and Warwickshire Research and Ethics Committee was obtained for this study (LREC 09/H1211/30).

For all women in the study, baseline data were recorded for histologic subtype, age, ethnic background, BMI, parity, menopausal status, medical history of hypertension or diabetes, use of exogenous hormones (hormone therapy, tamoxifen), and ultrasound measurement of endometrial thickness for postmenopausal women. For women using hormone therapy, we advised them to stop until endometrial regression was achieved and then it was restarted as necessary. Tamoxifen treatment was normally continued. Menopause was defined as a minimum of 12 consecutive months of amenorrhea for which there was no other obvious pathologic or physiologic cause. Missing data also were sought from primary care clinicians. The time from baseline histology until the last follow-up also was recorded for all patients.

The primary outcomes for this study were to identify predictors and to estimate their prognostic accuracy for regression and relapse of women with complex nonatypical hyperplasia or atypical complex hyperplasia treated with levonorgestrel-releasing intrauterine system or oral progestogens. For this assessment, the results of follow-up histologic examinations were classified as the following: complete regression–atrophy of glands, edematous fibrotic stroma, or pseudodecidualisation, with no evidence of hyperplasia; persistence or progression–failure to completely regress with evidence of complex nonatypical hyperplasia, atypical complex hyperplasia, or carcinoma; or relapse–failure to remain in regression with evidence of complex nonatypical hyperplasia, atypical complex hyperplasia, or carcinoma. The secondary outcomes we studied were the time interval from treatment initiation to complete regression and from regression to

relapse during follow-up. For the outcome of regression, we included all women with complex nonatypical hyperplasia or atypical complex hyperplasia diagnosed who underwent treatment with levonorgestrel-releasing intrauterine system or oral progestogens from August 1998 to December 2010 (n=344), and for the outcome of relapse until December 2007, to allow for at least 5 years of follow-up (n=219). All outcomes were evaluated with an intention-to-treat basis.

The baseline characteristics and outcomes for the levonorgestrel-releasing intrauterine system and oral progestogen groups were analyzed using Mann-Whitney *U* tests and Pearson χ^2 tests. For variables with a graphical Gaussian distribution, we report means and standard deviations and for skewed data medians, interquartile ranges, and overall ranges. We performed survival analysis using the Cox proportional hazards model because it accounts for variable duration of follow-up, censoring of participants, proportionality of event occurrence, and time to event.[10] We computed the proportional changes in hazard for predicting variables and presented event rates according to significant exposures. We calculated survival within our population by using Kaplan-Meier estimates for independent predictor variables.[11,12] Missing data were handled by complete case analysis for our outcomes (regression and relapse) and by multiple imputation for predicting variables.[13,14] All analyses were performed using STATA 12.1 (release January 2012).

RESULTS

Of the 655 women with complex nonatypical hyperplasia or atypical complex hyperplasia diagnosed over the 12-year study period, we excluded women managed for hysterectomy (n=249), managed by observation only (n=21), managed with other therapies than oral progestogens (n=14), or lost to follow-up after diagnosis (n=10). We included 361 women treated with progestogens. We had incomplete data regarding follow-up for 17 women and they also were excluded. Our follow-up rate for this outcome therefore was 95.3% (344/361). The final study group consisted of 250 women in the levonorgestrel-releasing intrauterine system group (229 with complex nonatypical hyperplasia and 21 with atypical complex hyperplasia) and 94 women in the oral progestogen group (81 with complex nonatypical hyperplasia and 13 with atypical complex hyperplasia). The median length of follow-up in the two groups was 58.8 months (interquartile range 38.4–96.4, range 12–148.2) for the levonorgestrel-releasing intrauterine system compared with 95.1 months (interquartile range 41.6–124.6, range 13.2–162) for the oral progestogen group. The duration of treatment with oral progestogens was 3 (29.8%, 28/94), 6 (63.8%, 60/94) or 12 months (6.4%, 6/94), and then the treatment was stopped. The most common type of progestogen therapy administered was norethisterone (50%), followed by medroxyprogesterone acetate (43%), dydrogesterone (2%), megestrol acetate (1%), and a combination of therapies (4%). Progestogen therapy was administered either cyclically (32%) or continuously (68%) at various doses. Three women with failed to regress with cyclical norethisterone 5 mg three times per day were administered another course of continuous norethisterone 10 mg twice per day. Since August 2008, we treated women opting for oral progestogens with norethisterone 5 mg three times per day or medroxyprogesterone 10 mg twice per day continuously for 6 months.

In the levonorgestrel-releasing intrauterine system group, 238 women completed the 5-year intended treatment. Six women requested removal of the levonorgestrel-releasing intrauterine system, five women reported spontaneous expulsion of the levonorgestrel-releasing intrauterine system, and one woman had a dislocated coil, which was inserted in the cervix.

Baseline clinical characteristics between women whose complex nonatypical hyperplasia regressed or persisted for each treatment group are shown in Table 1. The BMI was not available for 27 of 344 (7.8%) patients and also the endometrial thickness was not measurable in 9 of 162 (5.6%) of postmenopausal women. Regression of hyperplasia was achieved in 94.8% (237/250, 95% CI 91.3–96.9%) of women treated with levonorgestrel-releasing intrauterine system compared with 84% (79/94, 95% CI 75.3–90.1%) of women treated with oral progestogens. Regression was achieved more often for women with complex nonatypical hyperplasia (96.5%, 95 CI 93.3–98.2, 221/229 for levonorgestrel-releasing intrauterine system; 90.1%, 95% CI 81.7–94.9, 73/81 for oral progestogens) than for atypical complex hyperplasia (76.2%, 95% CI 54.9–89.4, 16/21 for levonorgestrel-releasing intrauterine system; 46.2%, 95% CI 23.2–70.9, 6/13 for oral progestogens). Women with complex nonatypical hyperplasia that failed to regress with levonorgestrel-releasing intrauterine system more often had a BMI of 35 or higher (HR 5.51, 95% CI 1.05–28.87; *P*=.043; Table 1). We did not identify significant predictors for women treated with oral progestogens or for women with atypical complex hyperplasia.

During the study period, 527 women had complex nonatypical hyperplasia or atypical complex hyperplasia diagnosed, and 265 were treated with progestogens. We have excluded women who did not achieve regression after progestogen treatment (n=24). We also have excluded women who did not accept long-term follow-up after their initial regression (n=18) or opted for hysterectomy (n=4). As a result, we have included 219

Table 1. Univariable Analysis for Prediction of Regression of Complex Hyperplasia Treated With Levonorgestrel-Releasing Intrauterine System or Oral Progestogens

	Levonorgestrel-Releasing Intrauterine System				Oral Progestogens			
Prognostic Variable	Hyperplasia Persisted (n=8)	Hyperplasia Regressed (n=221)	Hazard Ratio (95% CI)	*P*	Hyperplasia Persisted (n=8)	Hyperplasia Regressed (n=73)	Hazard Ratio (95% CI)	*P*
Age (y)								
Younger than 40	2 (25)	13 (5.9)	1		2 (25)	17 (23.3)	1	
40–60	6 (75)	166 (75.1)	0.54 (0.11–2.79)	.464	5 (62.5)	46 (60.3)	0.68 (0.13–3.66)	.657
Older than 60	0	42 (19)	NA	NA	1 (12.5)	14 (16.4)	0.7 (0.63–7.8)	.773
Parity								
Nulliparous	3 (37.5)	40 (18.1)	1		3 (37.5)	28 (34.3)	1	
1–2	3 (37.5)	104 (47.1)	0.36 (0.07–1.82)	.218	2 (25)	25 (36.2)	0.88 (0.14–5.38)	.892
3 or more	2 (25)	77 (34.8)	0.41 (0.06–2.58)	.342	3 (37.5)	28 (38.4)	1.32 (0.26–6.68)	.74
Ethnicity								
White	5 (62.5)	174 (78.7)	1		6 (75)	54 (74)	1	
Asian	0	27 (12.2)	NA	NA	1 (12.5)	9 (12.3)	1.04 (0.12–8.79)	.971
Other	3 (37.5)	20 (9.1)	0.87 (0.16–4.63)	.868	1 (12.5)	10 (13.7)	0.73 (0.09–6.11)	.772
Diabetes	1 (12.5)	34 (15.4)	1.13 (0.14–9.39)	.912	1 (12.5)	11 (15.1)	0.48 (0.06–4.02)	.502
Hypertension	1 (12.5)	77 (34.8)	0.58 (0.07–4.87)	.62	3 (37.5)	20 (27.4)	1.83 (0.43–7.75)	.411
Menopause	4 (50)	112 (50.7)	2.08 (0.46–9.43)	.34	2 (25)	25 (34.3)	0.69 (0.14–3.43)	.647
Hormone therapy or tamoxifen use	2 (25)	44 (19.9)	2.5 (0.48–13)	.277	0	11 (15.1)	NA	NA
BMI 35 kg/m^2 or higher	5 (62.5)	65 (31)	5.51 (1.05–28.87)	.043	4 (57.1)	15 (24.6)	2.4 (0.54–10.79)	.252
Endometrial thickness more than 9 mm	1 (20)	88 (46.8)	0.25 (0.03–2.36)	.227	4 (57.1)	28 (48.3)	1.24 (0.28–5.57)	.779

CI, confidence interval; NA, not applicable; BMI, body mass index.
Data are n (%) unless otherwise specified.

women in our study analysis of relapse, of whom 153 were treated with levonorgestrel-releasing intrauterine system (142 with complex nonatypical hyperplasia and 11 with atypical complex hyperplasia) and 66 were treated with oral progestogens (60 with complex nonatypical hyperplasia and 6 with atypical complex hyperplasia). The median follow-up in the two groups was 67 months (interquartile range 50.4–103.5, range 14.5–146.4) for the levonorgestrel-releasing intrauterine system group and 96.8 months (interquartile range 62.3–122, range 6–151.5) for the oral progestogen group. The relapse rate after levonorgestrel-releasing intrauterine system treatment was 13.7% (95% CI 9.2–20.1, 21 of153) and 30.3% (95% CI 20.6–42.2, 20/66) for women treated with oral progestogens. Relapse occurred less often for women with complex nonatypical hyperplasia (12.7%, 95% CI 8.2–19.2, 18/142 for levonorgestrel-releasing intrauterine system; 28.3%, 95% CI 18.5–40.8, 17/60 for oral progestogens) than with atypical complex hyperplasia (27.3%, 95% CI 9.7–56.6, 3/11 for levonorgestrel-releasing intrauterine system; 50%, 95% CI 18.7–81.2, 3/6 for oral progestogens).

Women with relapse of complex nonatypical hyperplasia in the levonorgestrel-releasing intrauterine system group were more often diabetic (33.3% compared with 11.3%, HR 2.91, 95% CI 1.09–7.76; $P=.033$; Table 2), had an endometrial thickness more than 9 mm (75% compared with 45.7%, HR 3.35, 95% CI 1.1–10.4; $P=.037$), and more often had a BMI 35 or higher (82.4% compared with 25%, HR 13.37, 95% CI 3.8–46.7; $P<.001$). In multivariate analysis of women with complex nonatypical hyperplasia treated with levonorgestrel-releasing intrauterine system, BMI 35 or higher was found to be a strong independent predictor of relapsed endometrial hyperplasia (HR 18.93, 95% CI 3.93–91.15; $P<.001$; Table 3). The cumulative event rates in Figure 1 show that only 3.3% of those women with BMI less than 35 will experience relapse of their complex

Table 2. Univariable Analysis for Prediction of Relapse of Complex Hyperplasia Treated With Levonorgestrel-Releasing Intrauterine System or Oral Progestogens

	Levonorgestrel-Releasing Intrauterine System				Oral Progestogens			
Prognostic Variable	Hyperplasia Relapsed (n=18)	Hyperplasia Regressed (n=124)	Hazard Ratio (95% CI)	*P*	Hyperplasia Relapsed (n=17)	Hyperplasia Regressed (n=43)	Hazard Ratio (95% CI)	*P*
Age (y)								
Younger than 40	0	8 (6.5)	1		2 (11.8)	10 (23.3)	1	
40–60	14 (77.8)	97 (78.2)	NA	NA	11 (64.7)	27 (62.8)	2.47 (0.55–11.18)	.239
Older than 60	4 (22.2)	19 (15.3)	NA	NA	4 (23.5)	6 (13.9)	3.18 (0.58–17.4)	.182
Parity								
Nulliparous	3 (16.7)	20 (16.1)	1		6 (35.3)	15 (34.9)	1	
1–2	10 (55.6)	56 (45.2)	0.94 (0.26–3.45)	.931	7 (41.2)	15 (30.2)	1.19 (0.4–3.56)	.749
3 or more	5 (27.8)	48 (38.7)	0.68 (0.16–2.86)	.601	4 (23.5)	15 (34.9)	0.62 (0.18–2.21)	.464
Ethnicity								
White	18 (85.7)	109 (83.2)	1		9 (47.4)	40 (83.3)	1	
Asian	2 (9.5)	13 (9.9)	1 (0.23–4.37)	.995	6 (31.6)	6 (6.3)	4.36 (1.54–12.36)	.006
Other	1 (4.8)	9 (6.9)	0.59 (0.08–4.44)	.61	4 (21)	5 (10.4)	2.29 (0.7–7.45)	.169
Diabetes	6 (33.3)	14 (11.3)	2.91 (1.09–7.76)	.033	4 (23.5)	4 (9.3)	1.96 (0.64–6.01)	.24
Hypertension	9 (50)	41 (33.1)	2.33 (0.92–5.9)	.075	5 (29.4)	13 (30.2)	1.43 (0.5–4.07)	.508
Menopause	9 (50)	61 (49.2)	1.1 (0.43–2.77)	.847	7 (41.2)	10 (23.3)	1.98 (0.75–5.21)	.165
Hormone therapy or tamoxifen use	1 (5.6)	29 (23.4)	0.16 (0.02–1.22)	.078	3 (17.7)	6 (14)	1.19 (0.34–4.16)	.781
BMI 35 kg/m^2 or higher	14 (82.4)	29 (25)	13.37 (3.83–46.69)	<.001	5 (41.7)	9 (25.7)	1.67 (0.53–5.27)	.381
Endometrial thickness more than 9 mm	12 (75)	48 (45.7)	3.35 (1.08–10.4)	.037	6 (40)	16 (48.5)	0.9 (0.32–2.54)	.844

CI, confidence interval; NA, not applicable; BMI, body mass index.
Data are n (%) unless otherwise specified.

nonatypical hyperplasia during long-term follow-up compared with 32.6% of women with BMI 35 or higher. One woman in the former group that experienced relapsed by 52 months had a BMI of 34.2 and, in this dataset, after 24 months from diagnosis, no woman with BMI less than 34 experienced relapse after initial regression with levonorgestrel-releasing intrauterine system.

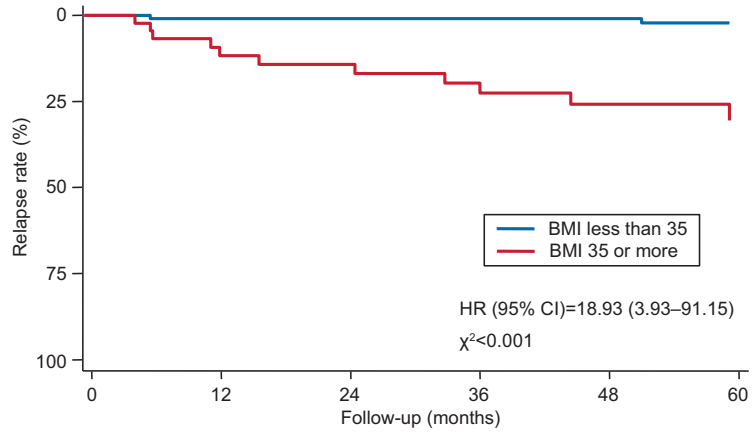
DISCUSSION

In this study, we found that BMI 35 or higher is strongly associated with relapse of complex nonatypical hyperplasia after initial regression with levonorgestrel-releasing intrauterine system treatment. This is independent of the presence of diabetes or endometrial thickness in these women. This study also finds weak evidence that BMI 35 or higher is associated with failure to regress

Table 3. Multivariable Analysis For Prediction of Relapse of Complex Hyperplasia Treated With Levonorgestrel-Releasing Intrauterine System

	Levonorgestrel-Releasing Intrauterine System (n=142)	
Prognostic Variable	Hazard Ratio (95% CI)	*P*
Diabetes	0.99 (0.32–3.11)	.991
BMI 35 kg/m^2 or higher	18.93 (3.93–91.15)	<.001
Endometrial thickness more than 9 mm	2.73 (0.82–9.16)	.103

CI, confidence interval; BMI, body mass index.



Cumulative event rates of relapse/total n by fixed time points (%)

BMI	Relapse at 12 months	Relapse at 24 months	Relapse at 36 months	Relapse at 48 months	Relapse at 60 months	Relapse at more than 60 months
BMI less than 35 (n=90)	1/90 (1.1)	1/90 (1.1)	1/90 (1.1)	1/90 (1.1)	2/90 (2.2)	3/90 (3.3)
BMI 35 or more (n=43)	4/43 (9.3)	6/43 (14)	9/43 (20.9)	10/43 (23.3)	11/43 (25.6)	14/43 (32.6)
Total (n=133)	5/133 (3.8)	7/133 (5.3)	10/133 (7.5)	11/133 (8.3)	13/133 (9.8)	17/133 (12.8)

Fig. 1. Kaplan-Meier survival curves for all events of complex hyperplasia relapse in women treated with the levonorgestrel-releasing intrauterine system. BMI, body mass index; HR, hazard ratio; CI, confidence interval.
Gallos. Prognosis of Endometrial Hyperplasia. Obstet Gynecol 2013.

complex nonatypical hyperplasia when treated with levonorgestrel-releasing intrauterine system. No predictors for regression or relapse for women treated with oral progestogens and for women with atypical complex hyperplasia initially diagnosed were identified.

We previously have described that the levonorgestrel-releasing intrauterine system has been used to treat endometrial hyperplasia and early-stage endometrial cancer, and has been found to be more successful treatment for women with endometrial hyperplasia than oral progestogens.[5–7,15] Oral progestogens were prescribed normally for 6 months and this may not be enough to treat endometrial hyperplasia; levonorgestrel-releasing intrauterine system is administered for 5 years, which could explain its success in treating endometrial hyperplasia. It induces initial regression more often than oral progestogens, and women are less likely to experience relapse during follow-up compared with those using oral progestogens.[6,7] However, relapse is common with both therapies and long-term follow-up is suggested.[15] From this study we can conclude that not all women need long-term follow-up when treated with levonorgestrel-releasing intrauterine system. The majority of women can be safely reassured that relapse is rare. The women who would benefit from long-term follow-up are women with BMI 35 or higher, because almost one out of three will experience relapse. The reason appears to be that the excess of endogenous estrogens persists over time and takes a toll in the antagonism with the levonorgestrel of the levonorgestrel-releasing intrauterine system. The hypothesis of excess body weight causing endometrial proliferation through estrogen excess and chronic hyperinsulinemia is not new and has biologic plausibility.[16] This suggests that this modifiable risk factor for endometrial hyperplasia may require further intervention to prevent relapse.

The prospective cohort design for women treated with levonorgestrel-releasing intrauterine system with long-term follow-up allows the accurate estimation of the predictive ability of clinical characteristics to predict regression or relapse. We involved primary care clinicians in the data collection and follow-up, and this resulted in our high follow-up rate and our dataset with few missing data. We have measured many variables that may confound our results and we have adjusted our estimates when necessary. Unfortunately, we did not engage in repeated measures of variables during follow-up that may differ from the baseline. For example, we did not monitor the BMI during the follow-up and only values at baseline were used for our analysis. The majority of the predictors reported in our study have not been found to be associated with regression or relapse. However, our study had less than 80% power for avoiding type II error and there is a high likelihood that the predictors we have investigated may represent false-negative results. Specifically, for women treated with oral progestogens or with initial diagnoses of atypical

complex hyperplasia, our sample size is particularly small to draw conclusions about the predictive ability of the exposures investigated.

This study has implications in clinical practice because it aids prognosis and helps decide a strategy for surveillance of women with complex nonatypical hyperplasia. We have suggested that all women with complex nonatypical hyperplasia should be followed-up for at least 24 months to establish if regression occurs. After initial regression after 24 months, we suggest long-term surveillance for women with levonorgestrel-releasing intrauterine system and BMI 35 or higher for another 60 months (5 years), resulting in a total of 7 years of follow-up. Women treated with oral progestogens should be followed-up for another 48 months because relapse is more common, but no woman experienced relapse after this cut-off of a total of 6 years.[7] We cannot make conclusions on the follow-up for atypical complex hyperplasia from this study, but the risks for failure to regress and relapse are likely to be higher and long-term follow-up is advised. Our experience requires external validation in other institutions to ensure our findings can be generalized and applied. Future research should focus on biomarkers that could aid the prognostic ability of predictors such as BMI and improve its accuracy.

REFERENCES

1. Reed SD, Newton KM, Clinton WL, Epplein M, Garcia R, Allison K, et al. Incidence of endometrial hyperplasia. Am J Obstet Gynecol 2009;200:678–6.
2. Kurman RJ, Kaminski PF, Norris HJ. The behavior of endometrial hyperplasia. A long-term study of "untreated" hyperplasia in 170 patients. Cancer 1985;56:403–12.
3. Gallos ID, Ofinran O, Shehmar M, Coomarasamy A, Gupta JK. Current management of endometrial hyperplasia–a survey of United Kingdom consultant gynaecologists. Eur J Obstet Gynecol Reprod Biol 2011;158:305–7.
4. Trimble CL, Kauderer J, Zaino R, Silverberg S, Lim PC, Burke JJ, et al. Concurrent endometrial carcinoma in women with a biopsy diagnosis of atypical endometrial hyperplasia: a Gynecologic Oncology Group study. Cancer 2006;106:812–9.
5. Gallos ID, Shehmar M, Thangaratinam S, Papapostolou TK, Coomarasamy A, Gupta JK. Oral progestogens vs levonorgestrel-releasing intrauterine system for endometrial hyperplasia: a systematic review and metaanalysis. Am J Obstet Gynecol 2010;203:547–10.
6. Gallos ID, Devey J, Ganesan R, Gupta JK .Predictive ability of estrogen (ER), progesterone (PR), COX-2, Mlh1, and Bcl-2 expression for regression and relapse of endometrial hyperplasia treated with LNG-IUS: a prospective cohort study. Gynecol Oncol 2013 Apr 17. pii: S0090-8258(13)00236-9. doi: 10.1016/j.ygyno.2013.04.016. [Epub ahead of print].
7. Gallos ID, Krishan P, Shehmar M, Ganesan R, Gupta JK Relapse of endometrial hyperplasia after conservative treatment: a cohort study with long term follow up. Hum Reprod 2013 Mar 6 [Epub ahead of print].
8. Ferenczy A, Gelfand M. The biologic significance of cytologic atypia in progestogen-treated endometrial hyperplasia. Am J Obstet Gynecol 1989;160:126–31.
9. Weber AM, Belinson JL, Piedmonte MR. Risk factors for endometrial hyperplasia and cancer among women with abnormal bleeding. Obstet Gynecol 1999;93:594–8.
10. Lin DY, Wei JL. The robust inference for the Cox proportional hazards model. J Am Stat Assoc 1989;84:1074–8.
11. Cox DR. Regression models and life tables. J R Stat Soc 1972;34:187–220.
12. Klein JP, Moeschberger ML. Survival analysis: techniques for censored and truncated data. 2nd ed. New York (NY): Springer; 2003.
13. Rubin DB. A non-iterative algorithm for least squares estimation of missing values in any analysis of variance design. J R Stat Soc 1972;21:136–41.
14. Schafer JL. Analysis of incomplete multivariate data. Boca Raton (FL): Chapman & Hall/CRC; 1997.
15. Gallos ID, Yap J, Rajhkowa M, Coomarasamy A, Luesley DM, Gupta JK. Regression, relapse and live birth rates with fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia: a systematic review and metaanalysis. Am J Obstet Gynecol. 2012;204:266.e1–12.
16. Anderson B, Connor JP, Andrews JI, Davis CS, Buller RE, Sorosky JI, et al. Obesity and prognosis in endometrial cancer. Am J Obstet Gynecol 1996;174:1171–9.